Remarks

The Office Action dated July 3, 2008 has been carefully reviewed and the following comments are made in response thereto. In view of the following remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicant has cancelled claims 1 to 6 and 8. The pending claims were amended to recite methods of treating cancer. Specifically, claims 15 and 16 were amended to recite methods of treating cancer rather than an agent for use in the methods of treating cancer. Exemplary support to the amendments to claims 15 and 16 is found on page 17, lines 4 to 19 of the specification. No new matter has been added.

Applicant notes that the Examiner's rejection of claims 15 to 16 under 35 U.S.C. 112, first paragraph, mentions both a lack of enablement and written description (*see* page 4 of the Office Action). The rejection, however, clearly alleges that claims 15 to 16 lack written description (*see* page 4 of the Officer Action ("written description of the agent(s) should be disclosed")). Accordingly, Applicant has treated this rejection as being a written description rejection. Applicants request clarification on this matter by the Examiner.

The Rejections under 35 U.S.C. 112, second paragraph should be withdrawn

Claims 1 to 6, 15, and 16 were rejected under 35 U.S.C. 112, second paragraph for allegedly being indefinite. Without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicant has cancelled claims 1 to 6 thereby rendering the rejection of these claims moot. Furthermore, claims 15 to 16 were amended to recite methods of treating cancer (*i.e.* the claims were rewritten in method form). As amended, the term "agent" is no longer recited claims 15 and 16. Accordingly, Applicant requests withdrawal of the rejection of these claims.

The Rejections under 35 U.S.C. 112, first paragraph should be withdrawn

Claims 7 to 16 were rejected under 35 U.S.C. 112, first paragraph for alleged lack of enablement. As discussed above, claims 15 and 16 were also rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to comply with the written description requirement.

As the Examiner indicated, the specification is "enabling for treating cancer" (*see* page 2 of the Office Action). Accordingly, without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicant has amended the claims to recite methods of treating cancer. Therefore, Applicant

requests withdrawal of the lack of enablement rejection. Applicant reserves the rights to pursue claims directed to prevention of cancer.

Regarding the rejection of claims 15 and 16, as discussed above, these claims were amended to recite methods of treating cancer. Since these claims no longer recite the term "agent," Applicant requests withdrawal of the rejection of these claims.

The Rejection under 35 U.S.C. 102(b) should be withdrawn

Claims 1 to 16 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Coffin. Specifically, the Examiner alleges that the reference discloses all the features of the claims expressly or inherently. The Examiner further alleges that a *prima facie* case of anticipation has been established (*see* page 6 of the Office Action). Applicant respectfully disagrees.

As the Examiner is aware, anticipation requires that a prior art reference discloses every limitation of the claimed invention either explicitly or inherently. *In re Scherber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). However, inherent anticipation is appropriate only when disclosure of the reference must *necessarily* include the unstated limitation. *Transclean Corp. v. Bridgewood Servs.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002). When the reference is silent about an asserted inherent characteristic, such a gap in the reference may be filled with recourse to extrinsic evidence that *clearly* indicates the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Cont'l Can v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

Prior to discussing the merits of the rejection, Applicant notes that claims 1 to 6 and 8 were canceled without prejudice or disclaimer and for the sole purpose of advancing prosecution. Accordingly, the rejection of these claims is moot.

Applicant notes that as used herein the phrase recombinant HSV refers to a recombinant HSV that is replication deficient and that can only replicate in tumor cells.

Coffin fails to disclose all the limitations of the pending claims and therefore cannot anticipate the claims. The Office Action alleges that Coffin discloses a recombinant HSV that may express an immunomodulatory protein such as *e.g.* a cytokine (*see* page 6 of the Office Action) and that this virus may be used to treat cancer. Coffin fails to disclose the specific type of cytokine that may be expressed by the recombinant HSV (*i.e.*, IL-18). Furthermore, while Coffin discusses administration of the recombinant virus in much detail including *e.g.* suitable doses, carriers and diluents (*see e.g.* Coffin, paragraphs 51 to 53), Coffin fails to disclose co-administration of the recombinant HSV with a cytokine,

in particular co-administration of a recombinant HSV with IL-18 as required by the claims. Coffin also fails to disclose that two different cytokines may be co-administered. Coffin further does not disclose that IL-18 is administered systemically or that IL-12 is administered locally. Furthermore, Coffin cannot inherently disclose systemic administration of IL-18. The recombinant virus is inactive until it is inside the cancer cell leading to localized expression of IL-18.

Since Coffin fails to disclose co-administration of IL-18 and a recombinant HSV, the reference cannot anticipate claim 7. Since the reference cannot anticipate claim 7, the reference also cannot anticipate claims 9 to 14 because they further limit the subject matter of claim 7. In addition, the reference also fails to disclose local administration of IL-12 and systemic administration of IL-18. Thus, since Coffin fails to disclose local administration of a recombinant HSV that expresses IL-12 to a cancer cell and systemic administration of IL-18, the reference cannot anticipate claims 15 and 16.

Furthermore, Coffin does not necessarily include unstated limitations. There is no teaching, suggestion or other extrinsic evidence that indicate that Coffin *et al.* discloses (1) co-administration of a recombinant HSV with IL-18, (2) administration of a recombinant HSV with co-administration of IL-18 and IL-12 and (3) co-administration of IL-18 and a recombinant HSV that expresses IL-12. The mere disclosure of expression of a cytokine by a recombinant virus does not disclose or suggest co-administration of a recombinant virus and a specific enumerated cytokine as set forth in the claims. Accordingly, the Examiner cannot rely on the doctrine of inherency.

In light of the foregoing amendments and remarks, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. 102.

The Rejections under 35 U.S.C. 103(a) should be withdrawn

Claims 1 to 16 were rejected under 35 U.S.C. 103(a) as being allegedly obvious over Johnson *et al.* in view of Yamanaka *et al.* Specifically the Examiner alleges that since the art discloses that the combination of IL-12 and IL-18 is beneficial in treating tumors, those of skill in the art would be motivated to combine the disclosures of Johnson *et al.* and Yamanaka *et al.* and the consequently the claims are obvious (*see* page 7 of the Office Action). Applicant respectfully disagrees.

Prior to discussing the merits of the rejection, Applicant notes that claims 1 to 6 and 8 were canceled without prejudice or disclaimer and for the sole purpose of advancing prosecution. Accordingly, the rejection of these claims is moot.

Applicant submits that the pending claims are not obvious over Johnson *et al.* in view of Yamanaka *et al.* because those of skill in the art would not be motivated to combine the disclosures of

these references since the co-administration of IL-18 and a recombinant HSV produces unexpected results.

The Office Action indicates that Yamanaka *et al.* discloses that (1) local secretion of IL-12 could affect anti-tumor activity which is enhanced by systemic administration of IL-18 and that (2) IL-12 and IL-18 have a synergistic effect (*see* page 301, column 1)). Further, Yamanaka *et al.* shows that IL-18 when administered alone did not inhibit tumor growth (page 299, column 1; page 301, column 1 (systemic administration of IL-18 alone did not affect tumor growth)). Yamanaka *et al.* does not disclose or suggest that co-administration of IL-18 and recombinant HSV can be used for treatment of cancer. Yamanaka *et al.* does not disclose or suggest that IL-18 and IL-12 when co-administered with a recombinant HSV virus would exhibit an anti-tumor effect.

The Office Action alleges that Johnson *et al.* discloses methods of treating cancer with a recombinant HSV in which ICP47, γ34.5 and optionally the ICP6 regions are inactivated (*see* page 6 to 7 of the Office Action). Johnson *et al.* further discloses that the effect of the virus may be augmented if the virus also encodes nucleic acids encoding immunomodulatory proteins such as *e.g.* cytokines including "any of interleukins 1 to 15" (Johnson *et al.*, page 10, lines 25 to 30). Johnson *et al.* does not disclose or suggest that IL-18 would augment the effect of recombinant HSV. Johnson *et al.* also does not disclose or suggest the use of IL-12 locally and IL-18 systemically. In addition, Johnson *et al.* does not disclose or suggest co-administration of IL-18 and recombinant HSV.

As discussed, Yamanaka *et al.* observed that systemic administration of IL-18 alone did not affect tumor growth in *in vivo* studies in mice (*see* page 301, column 1). Thus, Yamanka *et al.* observed that IL-18 does have <u>not</u> an anti-tumor effect as tumor growth is a measure of anti-tumor activity. This observation is inconsistent with Yamanaka *et al.* indicating IL-18 allegedly has an anti-tumor effect *in vivo* (*see* page 301, column 1). These results indicate a high level of unpredictability of the art. As the Examiner is aware, the mere fact that references can be combined or modified does <u>not</u> render the resultant combination obvious unless the results would have been predictable to those of skill in the art (M.P.E.P. 2143.01). Given the high level of unpredictability in the art, those of skill in the art would not be motivated to combine the disclosures of Yamanaka *et al.* and Johnson *et al.*

Applicant has shown numerous unexpected results for (1) the co-administration of IL-18 and recombinant HSV and (2) the administration of recombinant HSV with localized administration of IL-12 and systemic administration of IL-18. In light of these unexpected results, the pending claims are not obvious.

Applicant demonstrated that, surprisingly, co-administration of IL-18 with a recombinant HSV has a remarkable anti-tumor effect (*see* Example 1, page 18, line 21 to page 19, line 25). Specifically, Applicant has shown that co-administration of IL-18 with a recombinant HSV has a remarkably improved anti-tumor effect when compared to IL-18 administration alone (*see* page 19, lines 14 to 24; Figure 1). The recombinant HSV used by Applicant (G47Δ) has deletions or in activations in the ICP47, γ34.5 and ICP6 regions (*see* page 9, lines 18 to 22).

This effect is particularly remarkable since the viral replication ability of recombinant HSV is not affected by systemic administration of IL-18. Those in the art would recognize that the recombinant HSV is only selectively able to replicate in cancer cells and that the replication of the virus causes destruction of the cancer cell (*see e.g.* specification, page 1, line 24 to page 2, line 5). As such, the use of recombinant HSV as a treatment to cancer is highly dependent on having an actively proliferating tumor. Since IL-12 and IL-18 are known to exhibit anti-viral activity, those of skill in the art would expect decreased replication of recombinant HSV. However, surprisingly, Applicant demonstrated that the viral replication capacity of a recombinant HSV is <u>not</u> affected by co-administration of IL-18. Specifically, in Example 5, Applicant has demonstrated that the enhancement of anticancer activity of recombinant HSV by co-administration of IL-18 does not have an effect on the viral replication capacity of the recombinant HSV (*see* Example 5, page 22, line 14 to page 23, line 5; Figure 5).

Furthermore, Applicant has surprisingly demonstrated that co-administration of IL-18 and a recombinant HSV results in systemic immunity (*see* Example 3, page 20, line 21 to page 21, line 20; Figure 3). Specifically, Applicant has shown that, even when systemic anti-tumor immunity is not seen for administration of IL-18 alone, systemic anti-tumor immunity is induced by the co-administration of IL-18 and recombinant HSV (*see* page 20, lines 16 to 20). Those of skill in the art would have expected to see no such systemic immunity. For example, Yamanaka *et al.* discloses that injection of IL-12 cells does not lead to acquisition of a systemic anti-tumor immune response (*see* page 301, column 1). Yamanaka *et al.* also only show a localized effect for systemic administration of IL-12 coupled to localized administration of IL-18. Yamanaka *et al.* also showed that IL-18 alone does not inhibit tumor growth (*see* page 301, column 1).

Applicant has also surprisingly demonstrated that anti-tumor activity of recombinant HSV is enhanced by co-administration of systemic IL-18 and local administration of IL-12 (*see* Example 8, page 25, line 4-page 27, line 11). Specifically, Applicant has demonstrated systemic enhanced systemic anti-tumor immunity (*see* page 25, lines 7 to 11). These results are contrary to the art; for example, Yamanaka *et al.* showed no enhanced systemic activity for IL-12.

In addition, Applicant has surprisingly shown that co-administration of recombinant HSV virus and IL-18 even have an anti-tumor effect independent from the immune response. Specifically, Applicant has shown that that co-administration of IL-18 and a recombinant HSV virus exhibited an anti-cancer enhancing activity on an intra-cerebral tumor, where it is difficult for immune effects to appear (*see* Example 7, page 24, line 14 to page 25, line 3).

Applicant has clearly demonstrated that co-administration of IL-18 and recombinant HSV virus has surprising unpredictable results. As discussed above, the prior art is highly unpredictable. The surprising results demonstrated by the Applicant are contrary to what would be expected in the art. Therefore, those of skill in the art would not be motivated to combine the disclosures of Johnson *et al.* and Yamanka *et al.* Specifically, the combination of Johnson *et al.* and Yamanaka *et al.* does not disclose or suggest that IL-18 alone can be co-administered with recombinant HSV. The references also provide no motivation to combine administration of IL-18 alone with recombinant HSV. The references also do not provide a reasonable expectation of success to combine administration of IL-18 alone with recombinant HSV. Those of skill in the art relying on Yamanaka would realize that IL-18 alone has no effects on cancer cells (*see e.g.* page 299, column 1), thus one would not expect that co-administration of IL-18 and recombinant HSV provides for increased anti-tumor activity. In addition, those of skill in the art would also not except that co-administration of IL-18 and IL-12 provides for systemic anti-tumor activity. Those of skill in the art would also not expect that co-administration of IL-18, IL-12 and recombinant HSV would result in systemic anti-tumor activity. Accordingly, the pending claims are not obvious over the cited art.

In light of the foregoing amendments and remarks, Applicant requests withdrawal of this rejection.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,
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